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Differences In Disease-Free Survival And Acute Toxcity Between African-American And Non-Latino White Men With Localized Prostate Cancer Treated With Intensity Modulated Radiation Therapy

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Differences in Disease-Free Survival and Acute Toxicity between African-American and non-Latino White Men with Localized Prostate Cancer Treated with Intensity Modulated Radiation Therapy

A Thesis Submitted to the
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Abstract

Purpose

To determine whether differences exist in biochemical disease-free survival (BDFS) and acute toxicity between African-American (AA) and non-Latino white (NLW) men with prostate cancer treated with intensity modulated radiation therapy (IMRT).

Methods and Materials

Between January 2000 and January 2008, 129 AA and 591 NLW men with clinically localized prostate cancer were treated with IMRT. Median follow up was 26.6 months for both groups. Kaplan-Meier analysis was used to compute rates of biochemical disease free survival. Chi-square analysis was used to compute rates of acute toxicity.

Results

No difference was found in three year biochemical disease free survival (BDFS) rates between AA vs. NLW men, p= 0.71. Three year BDFS rates were 92% for NLW men vs. 89% for AA men. Multivariate analysis showed that race was not an important predictor of BDFS (p=0.88), while the variables PSA (p=0.003) and Gleason score (p=0.01) were. AA men had a significantly lower rate of gastrointestinal (GI) toxicity of grade 2 than NLW men (p=0.014), 6% vs. 13%, respectively.

Conclusions

Our study shows no difference in BDFS rates between AA and NLW men treated with IMRT. AA men had a lower rate of grade 2 GI toxicity than NLW men.

Acknowledgements

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Introduction

Prostate cancer is the most common cancer in men and is the second-leading cause of cancer death for men in the United States after lung cancer (1). African-American men have the highest reported incidence and mortality from prostate cancer in the world (2). Although African-American men are less likely to participate in prostate cancer screening, they are diagnosed at greater frequency, at younger ages, with higher prostate specific antigen (PSA) levels, and with a higher grade of disease (2).

Radical prostatectomy is an excellent treatment for young, healthy patients with disease of favorable prognosis (1). For older patients with favorable prognosis, non-surgical options are often used, as they offer similar 5-year biochemical disease free survival when compared to prostatectomy. Many patients with poor prognosis are treated with three-dimensional conformal radiotherapy (3DCRT) or intensity modulated external beam radiotherapy (IMRT) in conjunction with adjuvant hormone therapy (3,4). The development of IMRT has allowed more precise dosimetry and thus smaller planning target volumes and margins. This has allowed sparing of normal tissue of the rectum and bladder, reducing toxicity and morbidity, but allowing for safe dose escalation (5).

Black men presenting with earlier clinical stage and treated with radical prostatectomy have been shown to be at slightly increased risk for biochemical disease recurrence and have higher initial PSA values (3). Several studies suggest a genetic difference in prostate cancer that occur in African-American men in the density and affinity of androgen receptors, in addition to higher testosterone levels (3). Several large clinical studies have reported significantly lower biochemical disease free survival rates in African Americans with early prostate cancer treated with surgery compared with non-

Latino whites treated with surgery (6,7). Whether black men are at increased risk of developing gastrointestinal and genitourinary complications has yet to be fully explored and determined. At least one large study found an increase in GU complications in AA men treated with implant compared with non-Latino whites (8). We examined BDFS and acute GI and GU complications in AA and NLW men in a large cohort of consecutively treated patients with clinically localized prostate cancer during an eight-year period.

Statement of Purpose Specific Hypothesis and Specific Aims of the Thesis

The primary aim of this thesis is to determine whether differences exist between African-American men and non-Latino white men with prostate cancer treated with intensity modulated radiation therapy with respect to biochemical disease-free survival and acute gastrointestinal and genitourinary toxicity. We predict that African-American men will have lower biochemical disease-free survival and higher rates of acute toxicity compared with non-Latino white men.

Methods and Materials

Data Collection

After approval from the Yale Human Investigational Committee, clinical information from all patients undergoing prostate IMRT administered by the Yale Department of Therapeutic Radiology at the Yale New Haven Hospital- Hunter Radiation Therapy Center (New Haven, CT) and Lawrence and Memorial Hospital Department of Radiation Oncology (New London, CT) from January 2000 through January 2008 was resptrospectively collected using the TrialDB Clinical Study Data Management System (9). Clinical information including diagnostic and prognostic information, tumor stage, all recorded PSA values, Gleason score, risk group, and patient and physician reported toxicity information were abstracted by a research assistant (AM). Any reported toxicity, regardless of whether it was due to a preexisting condition, was recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 guidelines (10).

Patient Characteristics

From 1/1/2000 to 1/1/2008, 742 consecutive patients with localized prostate cancer were treated with external beam radiotherapy. Race was classified by self-identification. Individuals self-identified as Latino (n=11), Asian (n=9), or Not Specified (n=2) were not considered for analysis. Of the AA and NLW men, 22 were excluded because of incomplete follow up. Therefore, 720 patients were available for BDFS analysis and the characteristics of these patients are listed on Table 1. 38 patients of the 720 patients were excluded in the acute toxicity analysis because of incomplete toxicity information. Median follow up was 26.6 months for AA and 26.6 months for NLW men.

For the purposes of this study, risk groups were determined by the National Comprehensive Cancer Network Guidelines (11). Groups were defined as follows: low risk, Stage<T2a and Gleason score ≤6, and PSA ≤10 ng/ml; high risk, stage T3 or Gleason ≥8 or PSA>20 ng/ml; intermediate-risk, all others.

Table 1: Patient Characteristics

Variable	Non-Latino White (n=591)	African American (n=129)	p
Age			<0.001
≤65	168 (28%)	65 (50%)	
>65	423 (72%)	64 (50%)	
Clinical Stage			0.06
T1-T2a	454 (77%)	111 (86%)	
T2b-T2c	71 (12%)	8 (6%)	
T3a-T3b	66 (11%)	10 (8%)	
Gleason Score			0.46
≤6	213 (36%)	54 (42%)	
7	260 (44%)	52 (40%)	
≥8	118 (20%)	23 (18%)	
Pretreatment PSA			0.29
≤10	415 (70%)	87 (67%)	
>10 to ≤ 20	121 (21%)	24 (19%)	
>20	55 (9%)	18 (14%)	
MSK Prognosis Group			0.23
Favorable	187 (32%)	31 (24%)	
Intermediate	249 (42%)	59 (46%)	
Poor	155 (26%)	39 (30%)	
Hormonal Therapy			0.86
Yes	137 (23%)	29 (23%)	
No	454 (77%)	100 (77%)	

IMRT Technique

A standard dose escalated prostate IMRT protocol was institutionally developed based on available literature and our own institutional analysis of daily setup error and

quality analysis parameters. All patients underwent 3D CT stimulation and treatment planning. The treating physician contoured the prostate in its entirety.

From January 2000 to June 2003, patients were initially treated with 3D conformal radiation followed by an IMRT boost. These patients received 66.6 Gy in 37 fractions of 1.8 Gy using a 3D conformal technique, followed by a 9 Gy boost (in 5 fractions of 1.8 Gy) using IMRT. The 3D conformal radiation was delivered to the physician contoured prostate plus a symmetric 1.5 cm margin. The IMRT boost was delivered to the prostate plus a 1.0 cm symmetric margin in all directions, except for a 0.6 cm posterior margin at the interface of the prostate and rectum.

From June 2003 until January 2008, patients undergoing prostate radiation (without pelvic radiation) were treated with IMRT through the entire treatment course. The planning treatment volume (PTV) was defined as the physician contoured prostate plus a symmetric 1.2 cm margin to encompass microscopic extension and prostate motion. The entire seminal vesicles were included at the discretion of the treating physician, though routinely the PTV included at least the proximal 1/3 of the seminal vesicles. This PTV was treated to 66.6 Gy in 37 daily fractions as the "primary plan", with dose prescribed to the entire PTV. As the patients approached the completion of the initial 66.6 Gy, they received a second CT treatment simulation, and a prostate "cone down" plan was developed based on this second CT stimulation. The patient then underwent 5 additional fractions of 1.8 Gy to a PTV defined as the contoured prostate plus a 1.0 cm margin in three dimensions, save for a margin of 0.6 cm at the posterior border with the rectum. There were no scheduled treatment breaks. Therefore, total dose to the prostate was 75.6 Gy in 42 fractions of 1.8 Gy.

An isocentric five-field technique with 18 MV photons was typically used, using institutionally standardized normal tissue constraints. D_{max} was constrained to 115% of prescribed dose. Rectal constraint for patients receiving 75.6 Gy was $D_{25} \leq 70$ Gy, with the 50% isodose line not covering the entire rectum, and the 90% isodose line covering half of the rectum width on a slice-by-slice inspection of the entire rectum. Deviations from the standard criteria were allowable when unavoidable and approved by the attending physician. All plans (including both "primary" and "cone down" plans) were presented at institutional chart rounds for clinical and dosimetric review.

Statistical Analysis, Definition of Biochemical Disease Free Survival

Biochemical disease free survival (BDFS) was calculated using the RTOG-ASTRO Phoenix Consensus definition of the date of biochemical failure (the date when the PSA reaches a level equal to or greater than 2 ng/ml above the post radiotherapy nadir) (12). There was no backdating allowed. Kaplan-Meir curves for BDFS were constructed for each ethnic group and prognostic group and compared with the log-rank test. Univariate and multivariate BDFS analysis was performed using Cox proportional hazards analysis. Differences in acute toxicity between ethnic groups were assessed using the Chi-square test. Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc, Cary, NC).

Contributions to Thesis Project

Steven Oh was at least partially responsible for the conception and design of the study, data collection and analysis, and drafting of the manuscript. The study was primary designed by Steven Oh, Dr.James Yu, Dr.Ayal Aizer, and Dr.Richard Peschel, the senior investigator of the study. The majority of data collection was performed by Anne

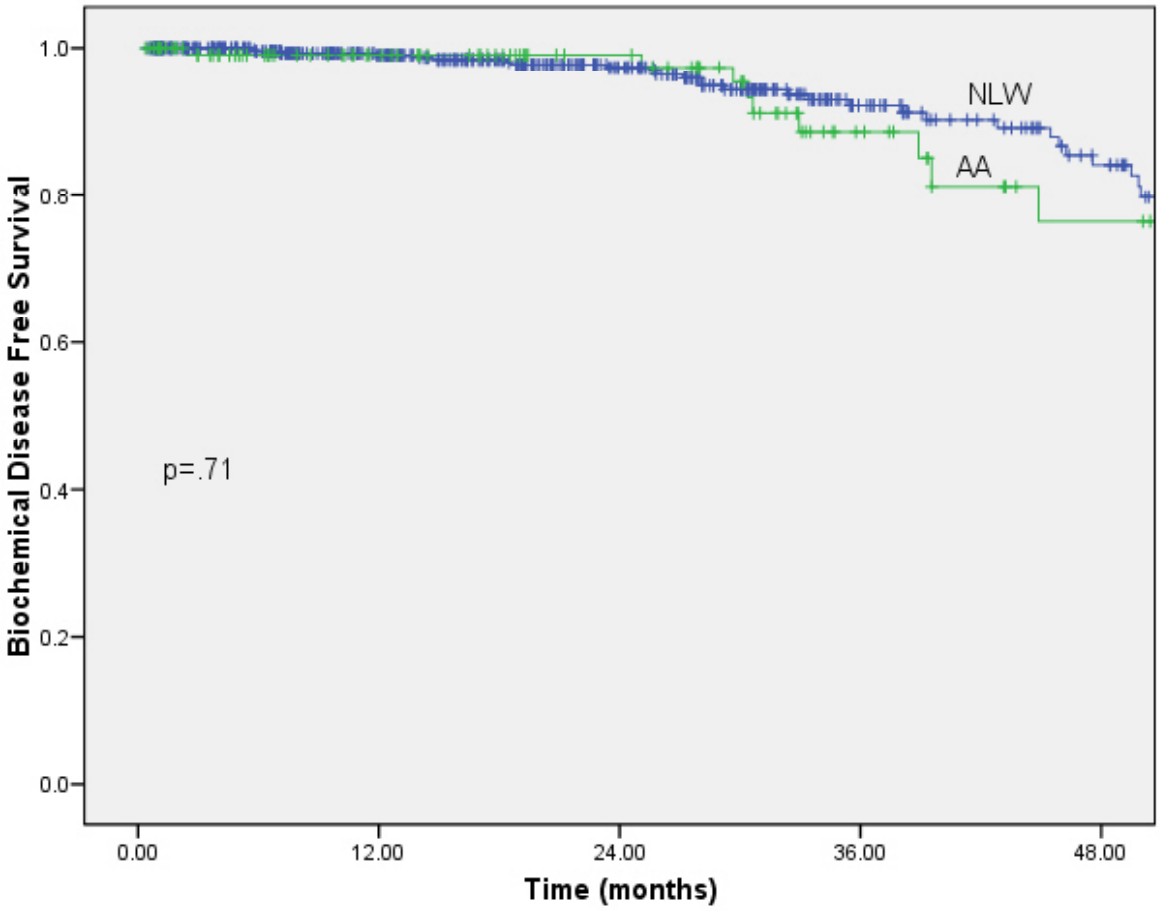
McKeon, although Steven Oh retrieved a portion of the data used in this study. Data analysis was performed by Steven Oh with statistical and software-related assistance provided by Dr.Ayal Aizer. The manuscript was prepared by Steven Oh with review and editing by Dr.James Yu and Dr.Richard Peschel.

Results

Biochemical disease Free Survival

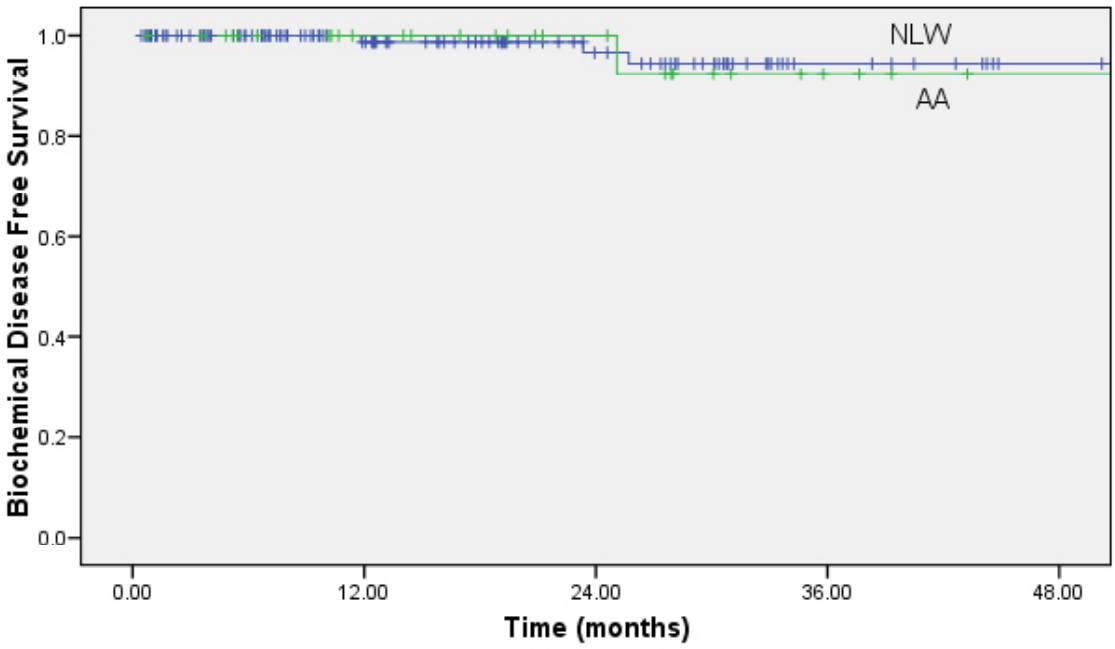
Three year BDFS was 89% (76% CI:87-95%) for AA men and 92% (95% CI: 87-95%) for NLW men. The log-rank test for difference in survival distribution by ethnicity was not significant, p= 0.71 (Figure 1).

Figure 1: BDFS for Whole Cohort



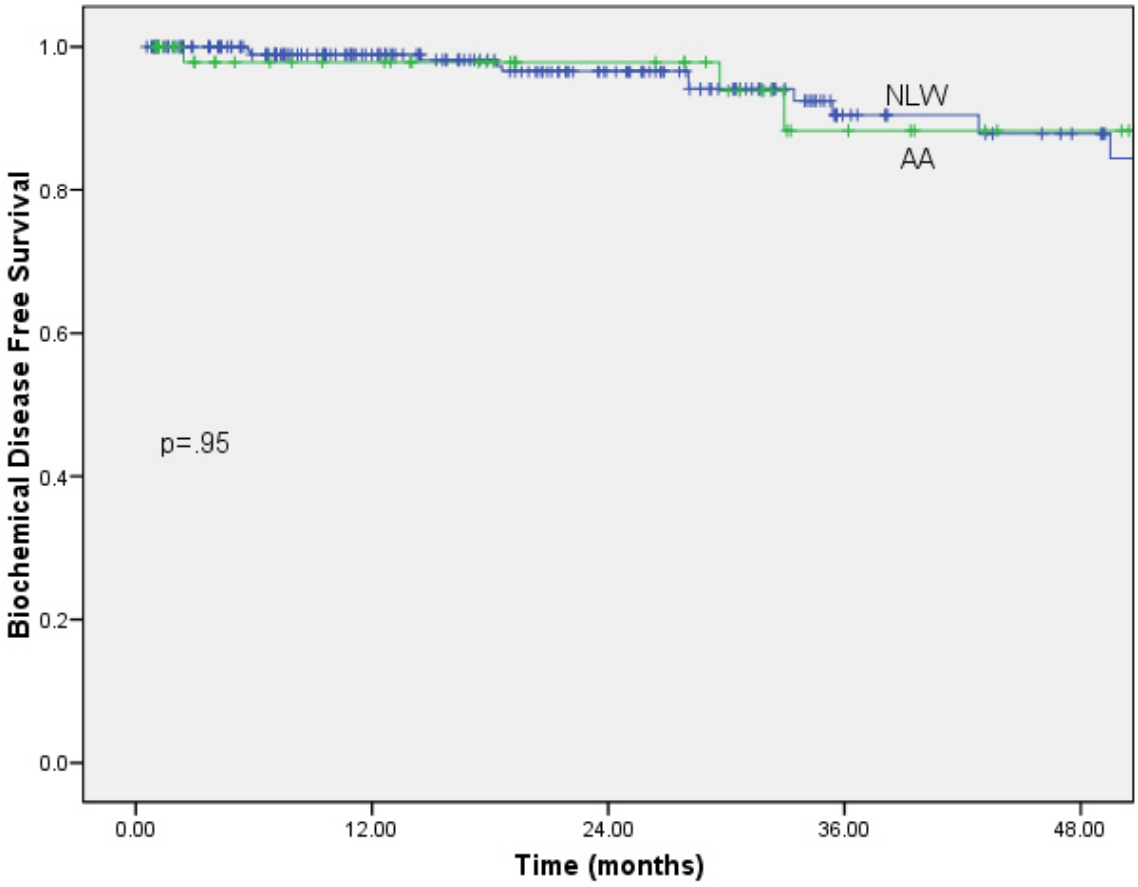
For the favorable group, three year BDFS was 92% (95% CI:57-99%) for AA men and 94% (95% CI:83-98%) for NLW men. The log-rank test for difference in survival distribution by ethnicity was not significant, p=0.75 (Figure 2).

Figure 2: BDFS for Favorable Prognostic Group



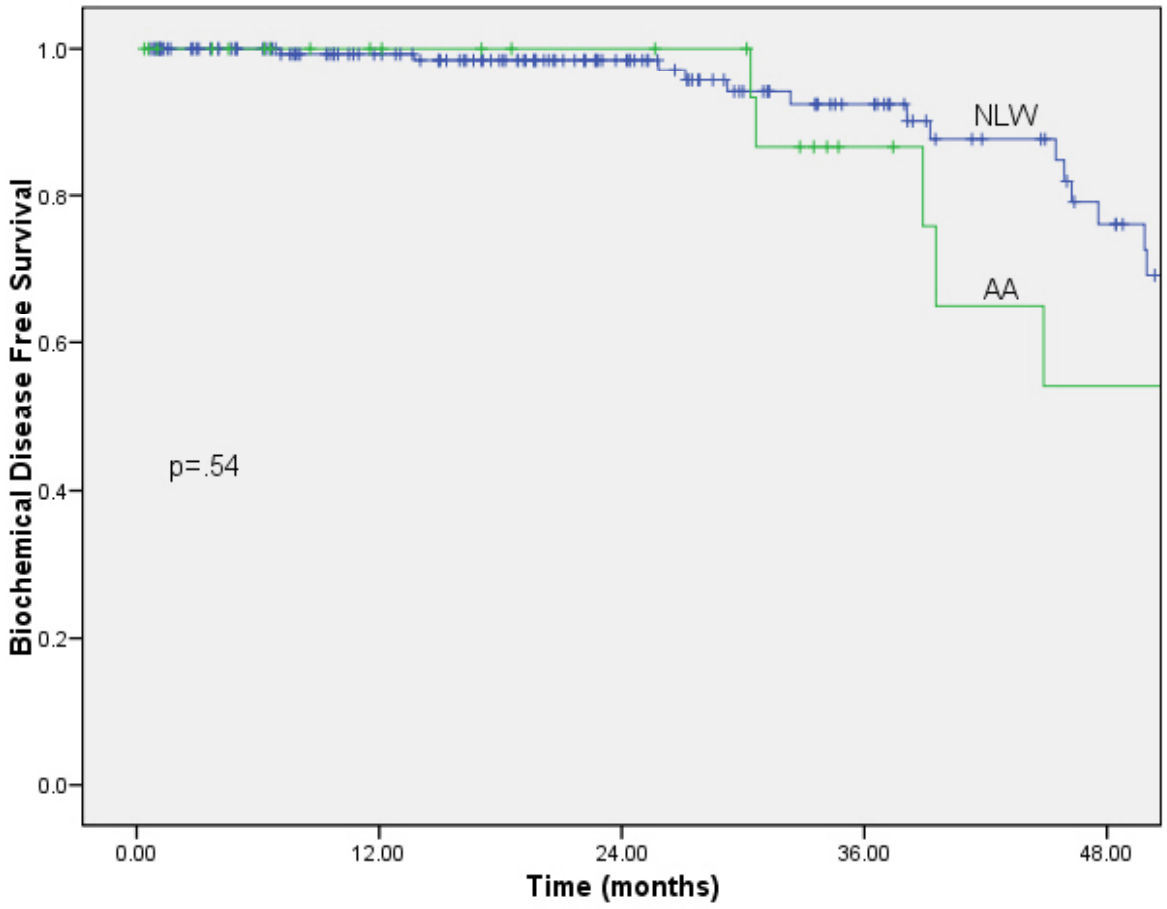
For the intermediate group, three year BDFS was 88% (95% CI:66-96%) for AA men and 90% (95% CI:81-95%) for NLW men. The log-rank test for difference in survival distribution by ethnicity was not significant, p=0.95 (Figure 3).

Figure 3: BDFS for Intermediate Prognostic Group



For the poor group, three year BDFS was 87% (95% CI:56-97%) for AA men and 92% (95% CI:83-96%) for NLW men. The log-rank test for difference in survival distribution by ethnicity was not significant, p=0.54 (Figure 4).

Figure 4: BDFS for Poor Prognostic Group



In a Cox proportional hazards analysis (Table 2), higher PSA (p=0.003) and higher Gleason score (p=0.01) were statistically significant predictors of biochemical failure. Race (p=0.88) was not a statistically significant predictor of biochemical failure.

Table 2: Unadjusted and Adjusted Analysis of Patient Characteristics and BDFS for Entire Cohort

Clinical Parameter	Unadjusted p	Unadjusted Hazard Ratio	95% CI	Adjusted p	Adjusted HR	95% CI
Age	0.3	0.98	0.94-1.02	0.22	0.98	0.94-1.02
Race	0.71	1.13	0.60-2.13	0.88	1.05	0.55-1.99
Clinical Stage	0.62	0.98	0.92-1.05	0.51	0.94	0.77-1.14
Gleason Score	0.01	1.43	1.09-1.87	0.01	1.45	1.09-1.93
Pretreatment PSA	0.003	1.01	1.00-1.02	0.003	1.01	1.00-1.02
Hormonal Therapy	0.5	1.28	0.63-2.60	0.92	0.96	0.46-2.02

Acute Toxicity

Acute toxicity from IMRT was defined as reported toxicity during or within 60 days of the end of radiation therapy (Table 3). GI toxicity of grade 2 was statistically lower in AA than NLW men, 6% vs. 13% (p=0.01). GI toxicity of grade 3 was 1% in AA men and 3% in NLW men, and this was not statistically significant (p=0.33). GU toxicity of grade 2 was 28% in AA men and 27% in NLW men, and this was not statistically significant (p=0.74). GU toxicity of grade 3 was 7% in AA men and 6% in NLW men, and this was not statistically significant (p=0.53).

Table 3: Acute Toxicity

Acute Toxicity	NLW (n=558)	AA (n=124)	p
GI Grade 2	75 (13%)	7 (6%)	0.014
GI Grade 3	14 (3%)	1 (1%)	0.329
GU Grade 2	148 (27%)	35 (28%)	0.737
GU Grade 3	32 (6%)	9 (7%)	0.531

Discussion

This study demonstrates no difference in biochemical disease free survival between African-American and non-Latino white men. Hispanic patients (n=11) and Asian patients (n=9) were excluded from analysis due to small numbers. In univariate and multivariate analysis, black race was not an independent predictor of BDFS among patients receiving IMRT.

In multivariate analysis, Cohen et al. report that black race predicted shorter disease-free survival among surgical patients, but not among radiation patients (6). The Cohen study merged data using the Surveillance, Epidemiology, and End Results (SEER) database files on 23,353 white patients and 2,814 black patients. This study thus comprises a significant number of patients and is far larger than this current series. Because this study used Medicare files, only patients greater than 65 years of age were included in this analysis. As black men are often diagnosed at a younger age than their non-white counterparts, it is possible that this study does not accurately portray the entire population given the age constraints. It is possible that there is a significant portion of black men who are diagnosed before the age of 65 and would likely have more aggressive disease. This raises the possibility that these men would increase the racial disparities in outcome and further increase the disease-free survival disparity among patients treated with radical prostatectomy. Furthermore, this raises the possibility that there could be differences between black and white men treated with radiation. Since this study does not include this subset of men diagnosed before the age of 65, it may be possible that a difference between these groups does in fact exist. It is important to note that the Cohen study pooled data from five SER regions including Atlanta, Connecticut,

Detroit, San Francisco, and Seattle. As these represent predominately urban areas, it is possible that this subset used for analysis is not representative of other rural areas. Thus, the Cohen study may be more of an indication of disparities between urban whites and black and not of the trends seen across the United States.

Several studies have shown that there are no disparities in BDFS for patients with localized prostate cancer treated with radiotherapy (13,14,15,16,17). In the Connell study from the University of Chicago, 418 black men and 475 white men were treated with conformal radiotherapy between 1988 and 1997. This study found that race was not an independent prognostic factor and that conformal radiotherapy was equally effective for black and white patients. Of note, this was an older series before the modern IMRT era. Despite using older radiation techniques, this series showed no differences between black and white men. Our study also finds no difference in three or five year BDFS between AA and NLW men.

Connell notes that black men presented with relatively advanced stages, PSA levels, and grades when compared to white men. This supports the notion that higher mortality rates in black men are a result of late diagnoses and the associated advanced nature of these tumors. Thus, socioeconomic factors such as access and availability to health care could be responsible for this difference in presentation. Other explanations for this difference include different diets and basal androgen levels. This series also notes that different familiar inheritance patterns and genetic variations could affect prostate carcinogenesis. Despite a difference at presentation, treatment efficacy was comparable for African-American and white men.

On the other hand, Latini et al. report a large disparity in 3-year actuarial DFS rates for prostatectomy patients between AA vs. NLW men, 83% vs. 69% (7). This study was also one of the first to include Latino men in the analysis. The Latini study pooled the results from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database and included 138 Latino men, 608 African-American men and 5,619 non-Latino white men. Interestingly, this study found that Latino men resembled African-American men on sociodemographic characteristics. However, Latinos were more similar to non-Latino white men on clinical presentation, treatment, received, and disease-free survival. This is of note because much of the literature points to differences in socioeconomics as a cause of racial disparities in outcomes. Some argue that differences in income and education may be responsible for poorer outcomes in black patients. However, the Latini study looked at several sociodemographic factors such as education, income, type of insurance, and relationship status. This analysis shows that Latino patients are similar to black patients in these sociodemographic factors. Despite this, black patients have higher rates of disease recurrence.

While some suggest that sociodemographic characteristics are responsible for worse outcomes in African-American men receiving surgery, our study finds no disparity in BDFS among radiation patients. This result is encouraging. One possible explanation for a lack of disparity in radiation patients treated at Yale is that our referral patterns reflect a community population rather than an inner city population. The city of New Haven is 38.8% AA while New Haven county is 12.2% (18). In our study, 18% of the patients were AA men and this reflects a community population rather than a true inner city population. It is possible that disparities were not present because AA and NLS were

of a similar sociodemographic background. However, Gondi et al. found an improved 5-year BDFS in AA versus NLW men with intermediate-risk prostate group in a racially diverse university population in New York City (19). Even in an inner city population, AA men did not have lower BDFS and in fact had superior 5-year BDFS when treated with radiotherapy. This study confirms the results of Cohen at al. that black race does not predict shorter BDFS in radiation patients and the reasons why black race is a predictor of shorter BDFS in surgery patients but not radiation patients should be further explored.

In order to better understand racial disparities in cancer care, it is helpful to consider other disease sites as well. Diffuse large B-cell lymphoma has been shown to have different presentations in black versus white patients. In a SEER database study by Shenoy et al., the outcomes of 38,522 patients with diffuse large B-cell lymphoma were investigated using the Surveillance, Epidemiology, and End Results database from 1992 to 2007 (20). This database used patients from 13 population-based registries including Connecticut, Hawaii, Iowa, New Mexico, Utah, Detroit, San Francisco/Oakland, Seattle/Puget Sound, Atlanta, Los Angeles, and San Jose/Monterey. Like many other cancer disease sites, black patients with diffuse large B-cell lymphoma were diagnosed at a younger age compared with white patients, 54 versus 65 years, respectively (20). Furthermore, a greater proportion of black patients presented with stage III/IV disease when compared with white patients, 52% versus 45% (20). 31% of black patients presented with B symptoms while 24% of white patients presented with B symptoms (20). Whites had a much higher rate of 5-year relative survival rate as compared to black patients, 54% versus 45% (20). Kaplan-Meir survival curves for diffuse large B-cell lymphoma patients demonstrated better survival among whites as compared with blacks.

Compared with whites, black patients had a higher mortality, with a hazard ratio of 1.12 (CI 1.04-1.1) (20).

A study by Nichols et al. investigated outcomes in black patients with early breast cancer treated with breast conservation therapy (21). In this retrospective study, 1231 consecutive patients greater than 40 years of age and with stage I-II invasive breast cancer were treated with lumpectomy and radiation therapy at the University of Chicago Hospitals between 1986 and 2004. 34% of patients were black and the remainder were Caucasian, Hispanic, or Asian. Black patients had a poorer 10 year overall survival compared with nonblack patients, 64.6% versus 80.8%. In addition, black patients had lower disease-free survival compared with nonblack patients, 58.1% versus 75.4%.

Nichols discusses that breast cancer mortality has been declining in all women since 1990, but the magnitude of this decrease has been greater for white than for black patients. Improvements in screening mammography and adjuvant therapy have helped to contribute to this decrease in mortality. However, the magnitude of this decrease has been a 2.4% yearly decline in Caucasian women versus 1.1% in African-American women. It is still unclear why this discrepancy exists. While some have noted that black women have been less likely than their Caucasian counterparts to use screening mammograms, more recently screening mammograms use has reached the same level in black and white women. This makes the underutilization of mammography less likely to explain these racial disparities.

Of note, this series also states that black patients are more likely to be classified as having lower socioeconomic status. Defining socioeconomic status is difficult and no consensus on the most suitable definition has been reached, though many account for

marital status, level of education, and income. Despite a lack of a clear consensus, Nichols notes that even when controlling for age, stage, and socioeconomic status, race is an independent indicator of breast cancer mortality. While many have stated that socioeconomic status is a contributing factor to racial disparities in breast cancer mortality, it appears that it is not the sole explanation of why these disparities continue to persist.

Recently, Du et al. performed an analysis using the linked National Longitudinal Mortality Study and Surveillance, Epidemiology, and End Results data to determine the effects of individual-level socioeconomic factors and racial disparities in receiving treatment and in survival. This group used health insurance, education, income, and poverty status to qualify individual-level socioeconomic factors. Health insurance was further categorized into employer health care, government, Medicare, private company, Medicaid, or uninsured. Education was classified into less than high school, high school graduate, or some education after high school. Family income was categorized into three categories including <$10,000, $10,000 to $34,999, and greater than $35,000. Poverty status was measured in terms of the ratio of the family income to the poverty threshold for a four person family and grouped into less than 100%, 100% to 400%, and greater than 400%. A total of the eight most common tumor sites were included and consisted of breast, colorectal, prostate, lung and bronchus, cervix, ovarian, urinary bladder, and melanoma of the skin.

Du found that the hazard ratio for cancer-specific mortality was significantly higher among black compared with whites (HR, 1.2, 95% CI 1.1-1.3) (22). After further controlling for socioeconomic factors and treatment, the hazard ratio was no longer

significantly higher for black patients compared with white patients (HR 1.0, 95% CI 0.9-1.1) (22). Another interesting finding of this study was that even after controlling for socioeconomic factors and patient and tumor characteristics, blacks were significantly less likely to receive cancer-directed surgery compared with whites, possibly because of a less favorable stage distribution at diagnosis (22). It is notable that this recent study showed that hazard ratios for all-cause and cancer-specific mortality among blacks compared with whites for 8 leading tumors combined lost statistical significance after adjusting for socioeconomic factors and treatment. However, it is still difficult to determine whether socioeconomic factors help explain racial disparities despite this study. Given that other studies have shown that even controlling for socioecononmic factors does not explain the large gaps in outcomes, it will be still be important to look for other causes and explanations. One possible reason that this study has shown that socioeconomic factors can explain disparities is that it carefully categorized and stratified individual factors such as health insurance, education, income, and poverty status. It may be that creating more complicated models of socioecnomic factors that incorporate more variables will explain more of the current disparities in cancer care.

A relevant point that Nichols brings up in his discussion is the prevalence of comorbid disease. A higher prevalence of comorbid disease along with obesity has been mentioned in the literature as a contributing factor in disparities in outcomes. Comorbid disease such as diabetes mellitus and cardiovascular disease can lead to an increase in mortality. It is possible that the comorbid disease is contributing to decreased overall survival and is an independent factor regardless of race or presence of breast cancer. However, race is still independently associated with breast cancer mortality when

controlling for the effects of comorbid disease. While the Nichols series also noted that black patients had a higher incidence of comorbid disease, it is important to note that comorbid disease was self-reported. This makes it unclear whether some important contributors to early mortality were omitted.

Perhaps one of the most interesting points brought up in Nichols' discussion is the role of biology with regards to racial differences in breast cancer. Several biological differences have been noted in breast carcinogenesis in African-American women. Tumors in black women have been noted more often be estrogen receptor and progesterone receptor negative. In addition, tumors tend to be of a higher grade and mitotic index. Alterations of p53 have also been noted. It is difficult to determine whether this in fact a different biological presentation in black women or if this is due to a later presentation in black women. It is possible that these biologic differences do indeed reflect an inherently more aggressive tumor phenotype.

In another series from the University of Chicago, racial disparities were noted for endometrial cancer. Connell et al. compared the outcomes of 70 black and 302 white women with endometrial carcinoma who underwent primary surgery at the University of Chicago Hospitals between 1980 and 1995 (23). Black women had higher grade tumors, less favorable histologic findings, more comorbid illnesses, and lower socioeconomic indices. Black women had worse 5-year disease-free survival than white women, 52.8% versus 75.2%. After controlling for pathologic and socioeconomic differences in multivariate analysis, race remained a significant prognostic factor.

Connell notes that numerous disparities exist between black and white women with endometrial cancer. Of note, endometrial carcinoma is diagnosed twice as frequently

in white women as in black women, but black women are approximately twice as likely to die from this disease (23). The age-adjusted mortality rate of endometrial cancer for black women is 6.0 per 100,000 versus 3.3 in white women (23). Several biologic differences have been noted and postulated to account for these racial disparities. For example, black women have been noted to have higher tumor grades and less favorable histologic findings. In the Connell series, black women did have more papillary serous tumors as compared to their white counterparts, 17.1% versus 6.6%, respectively. Furthermore, grade 3 tumors were nearly twice as frequent in black women versus white women, 31.4% versus 16.9%. Grade 1 tumors were in fact twice as frequent in white women as black women, 36.4% versus 17.6%. This series and previous literature note that differences in grade are present between these two groups. Differences have also been noted in p53 mutations in black women. Black women more frequently have p53 mutations than white women. However, it is still unclear whether this demonstrates more aggressive tumor biology or if this is a marker of more advanced disease. One of the most relevant findings is that despite controlling for biologic factors such as grade and unfavorable histologic patterns, race remains an important prognostic factor.

The University of Chicago experience clearly demonstrates racial disparities in outcomes between black and white women for both breast and endometrial cancer. One of the most puzzling pieces to this story is that these racial disparities do not hold true for prostate cancer. It is interesting to note that in the same population, prostate cancer is the notable exception for differences in outcome. It is unclear why this would be the case given that much of the literature shows worse outcomes for blacks with cancer, regardless of site.

While black men do present with a different biology compared to their white counterparts, notably higher Gleason scores and initial PSA values, race does not appear to be an independent prognostic factor. On the other hand, race continues to be an important prognostic factor for breast and endometrial cancer. An explanation for this exception remains elusive, though it has clearly been identified in numerous series that there are no differences in biochemical disease free survival between black and white men.

Racial disparities in cancer therapy remains an important area of investigation. In the early 1990s, these discrepancies were first identified in the literature. Since this disparity has been described, it is interesting to note whether improvements have been made after identifying this as an issue. Gross et al. used the SEER database to investigate this question. In this study, a cohort of patients was selected using the SEER-Medicare database for patients between the ages of 66 to 85 years and who had a primary diagnosis of colorectal, breast, lung, or prostate cancer from 1992 through 2002 (24). For all sites, black patients were less likely than white patients to receive therapy for cancer. Of note, definitive therapy for early stage prostate cancer was completed less often in black patients versus their white counterparts, 72.4% versus 77.2%. Unfortunately, there was no decrease in the magnitude of these racial disparities between 1992 and 2002.

One of the most pertinent findings in this study was that for all sites considered, black patients were less likely to receive cancer therapy. The final sample consisted of 143,512 patients and the most common cancer type was prostate cancer with over 82,000 patients analyzed. It is unclear why 5% less black men recieved definitive therapy for stage I prostate cancer. One of the most pressing questions from this data is whether this

is a result of access to health care or patient preference. Since both groups were offered therapy, it is possible that this difference is a result of patient choice. The fact that 5% less black patients chose definitive therapy could reflect a decision by black patients to not undergo therapy. While some may argue that black patients do not have the same access to health care, it is possible that black patients are choosing not to undergo therapy for a variety of reasons, including distrust of the medical system. It would be most helpful to know the reasons why some of these black patients chose not to receive treatment that their white counterparts chose to receive. One area of investigation that was not mentioned is whether a significant portion of the black community remains hesitant to receive treatment out of distrust of the medical community.

Consistent with the University of Chicago experience, the Gross study notes that black patients were more likely to reside in areas with lower median income and other measures of socioeconomic status. Despite controlling for this using several models, access and socioeconomic status did not entirely explain racial disparities in therapy. While access and socioeconomic status have been mentioned repeatedly as the culprit for racial disparities, these studies demonstrate otherwise. It is unfortunate to note that this study showed no improvement in racial disparities in the past ten years, despite identifying this as an issue. Despite efforts to increase awareness of racial disparities and increase access to health care over the past decade, black patients are still not receiving treatment to the same extent as their white counterparts.

Now that disparities have been noted in cancer care, what can be done to improve the gap that exists between the care that white and black patients receive? Regardless of disease, inequity in the delivery of health care leads to much worse outcomes for certain

groups, notably ethnic minorities and the poor. There are numerous barriers that cancer patients face such as the demands of work, family responsibilities, and emotional stress (25). These barriers are magnified for minorities and low-income patients who have limited access to basic necessities such as transportation and affordable childcare (25). In addition to these barriers, other barriers such as culturally specific health beliefs generate distrust of the health care system. Neighborhood-based infrastructural deficits associated with poverty can manifest in a lack of the basic personal means or social support to successfully navigate the complex world of cancer care (25).

In the past decade, therapies for cancer care have significantly improved with the advent of multimodality therapy. It is interesting to note that this has inevitably led to more complicated care that requires more coordination of care. In fact, as new technologies and therapies are developed, many at-risk groups are left behind and the gap in health care delivery increases. Thus, already disadvantaged patients do not benefit from complex treatment innovations that otherwise are improving health outcomes. The complexity of care in fact leaves many from lower socioeconomic status groups behind, as they are unable to coordinate their own care and find the means of transportation or income to initiate and complete their multimodality care.

It is important to note that the communities that many African-American patients live in are very different from those of their white counterparts. The social infrastructure in place can also be a cause of racial disparities. In many black neighborhoods, the doctors who provide care often have less training and access to state of the art clinical resources. A lack of infrastructure and community for support during illness are key factors that may be contributing to the persistence in health care outcomes disparities.

Recently, the National Cancer Institute initiated the Cancer Disparities Research Partnership (CDRP) to develop clinical trials and a research infrastructure within communities that serve patient populations facing health care disparity (25). Traditionally, black patients have not had the same access to clinical trials and thus cutting edge cancer treatment as their white counterparts. Furthermore, this grant implemented patient-navigator programs to address the fundamental process-of-care disconnects and barriers to care that black patients face.

The patient-navigator concept was first described by Harold Freeman and implemented in Harlem, NY to address community based barriers as well as distrust of the medical system. It consists of a culturally and linguistically appropriate individual who supports a patient through the process of care. These individuals can provide support and more importantly coordination of care. In addition, they are able to explain the rationale and benefit of participation in clinical trials. These navigators in the community are also able to elucidate barriers and address all of the barriers that are manifestations of the infrastructural and societal deficits in the underserved community that increase a patient's likelihood of not complying with treatment and follow-up regimens (25).

The initial experience of the CDRP Urban Latino African American Cancer Disparity program in South Los Angeles, California has helped identify several barriers facing patients. Of note, community based structural deficits such as lack of transportation and other financial resources have proved to limit successful and timely completion of cancer treatment. This group has also noted that the fear of cancer and the morbidity of treatment has limited compliance with care regimens. Interestingly, the constraints on caregiver support have also contributed to deficits in care. These patient

navigator systems have the potential to greatly enhance patient compliance and thus narrow the gap in racial disparities. It is important to realize that for the disadvantaged patient, navigating the health care system can be daunting and close to impossible. Having a source of support to coordinate multidisciplinary care can be essential for completion of therapy.

While the patient navigator system is one model to improve outcomes and decrease disparities, there are many barriers that prevent it from being successful nationwide. Notably, such programs are expensive to hire and train such navigators. A randomized clinical trial would likely be necessary in order to demonstrate that black patients have improved outcomes in survival with the help of a navigator. This is most likely the only scenario that would justify funding for this program throughout the country to help eliminate racial disparities in cancer care.

Ultimately, disparity is about poverty and the lack of infrastructure to meet the needs of disadvantaged patients (25). Establishing the necessary infrastructure to narrow the disparity gap is clearly an important and essential goal of future health care. Yet the exact means by which to set up infrastructure remains uncertain. A key factor that is a source of current difficulties is the United States health care system. The current system is a mix of government insurance and private insurance, as well as no insurance. Insurance companies are not motivated by improving quality and decreasing disparities. Instead, they seek to limit costs and emphasize cost control. Setting up the necessary infrastructure for the African-American community to help eliminate disparities will require a significant investment in capital. Many today point to the large expenses spent on American health care, especially relative to the nation's gross domestic product. Some

would consider our current health system to have many areas of unnecessary spending and waste. However, members of the disadvantaged community are not the recipients of this unnecessary health care service. In fact, they are the ones that often need it the most. In the long run, investing in infrastructures necessary to support the health of minority communities will not only decrease the gap in cancer outcomes, but it will improve costs as well. Efforts at screening and early detection of disease will most likely decrease health care spending by treating diseases at earlier stages when less drastic and costly interventions are required. Establishing the infrastructure to promote health in communities will also decrease comorbid disease and its associated costs.

One of the greatest challenges of cancer care in the coming years will be to narrow the gap in outcomes between African-American and white patients. Disparities have been documented for over the past decade. While some progress has been made in documenting these differences for various sites, the disparities still persist. It will be up to future generations of physicians and leaders to close this gap.

Despite the persistence in racial disparities between black and white patients with cancer, our study as well as others demonstrate that there are in fact no differences in overall survival between black and white patients with prostate cancer treated with radiation therapy. Black men are diagnosed at later stages of disease and often with more biologically aggressive disease but seem to fare similarly to their white counterparts after receiving radiation therapy. This provides hope that disparities are not inevitable and that they can be addressed.

One question that remains to be answered is why these disparities do not exist for black patients treated with radiation, and yet black patients treated with radical

prostatectomy fare worse than their white counterparts. It is puzzling that in the same racial group and disease site, one modality of treatment would result in racial disparities in outcome while the other does not. If access to health care is indeed a barrier for black patients, it would be expected that patients that receive radiation would fare worse than those who receive surgery. Radical prostatectomy is a one day procedure requiring hospitalization. On the other hand, a course of radiation requires multiple treatments over weeks and one would expect that black patients with difficulty accessing health care and transportation would miss more treatments or not complete treatment. This seems not be the case.

No differences in acute GU toxicity of either grade 2 or 3 were found between AA and NLW men treated with IMRT. In contrast, Chen et al. found an increase in GU complications in AA men treated with brachytherapy compared with NLW men (8). Acute GI toxicity of grade 2 was less in AA men than NLW men, but no differences were found in toxicity of grade 3. It is possible that AA men have lower rates of GI toxicity of grade 2 than NLW men. Another possible explanation is that AA men are underreporting GI toxicity to their physicians because they are uncomfortable mentioning this. Once more serious complications arise, such as grade 3 toxicity, they may be more open to discussing this with their physicians. Whether there is underreporting of GI toxicity or if AA men have lower rates of acute GI toxicity should be further explored.

An analysis of acute toxicity is important because quality of life is an important consideration in survivorship. Many studies have described racial disparities in overall survival and biochemical disease free survival between African-American men and white men. However, acute toxicity has not been widely reported prior to this study. It is

important to note that acute toxicity influences how patients rate the quality of their life, especially immediately after treatment. Because many patients are successfully treated and cured with modern therapy for prostate cancer, acute toxicity and side effects remain an important issue. As patients have numerous treatment options ranging from radical prostatectomy, brachytherapy, radiation therapy, or cryotherapy, it is important to note how side effect profiles may differ. Many patients are survivors for years after therapy and judge the success of their therapy often on the side effects they face or are left with. Acute and long-term toxicity will ultimately influence a patient's quality of life and also their willingness to recommend their treatment to others. It is encouraging to note that black men do not suffer from increased side effects immediately after therapy. This is also in contrast to the Chen study that demonstrated that African-American men suffer from increased GU toxicity following brachytherapy (8). Further studies are warranted to determine whether this lack of racial disparity in acute toxicity persists with IMRT in other series from other institutions.

A major strength of this study is that it is one of the first to report acute toxicity differences between NLW and AA men who receive IMRT for prostate cancer. Limitations include the weaknesses of any retrospective study, including the fact that patients were excluded because of incomplete follow up or missing toxicity information. Furthermore, this study represents the results of only a single institution. Work needs to be done to explore acute toxicities in patients of other ethnicities as well. Because of small numbers, we excluded Latino and Asian patients from this analysis.

In conclusion, our study of biochemical disease-free survival shows no difference in outcomes for African-American versus non-Latino white men. African-American men

have a lower rate of acute GI toxicity of grade 2 with no differences in rate of GI toxicity of grade 3 or GU toxicity of grade 2 or 3. Further studies are needed to determine if African-American men have a lower rate of acute GI toxicity or if this is due to underreporting.

References

1. Peschel RE, Colberg JW. Surgery, brachytherapy, and external-beam radiotherapy for early prostate cancer. Lancet Oncol 2003; 4: 233-41.

2. Hamilton RJ, Aronson WJ, Presti JC, et al. Race, biochemical disease recurrence, and prostate-specific antigen doubling time after radical prostatectomy. Cancer 2007; 110: 2202-9.

3. D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs. radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004; 292 (7): 821-827.

4. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomized trial. The Lancet 2002; 360: 103-108.

5. Guerrero Urbano MT, Nutting CM. Clinical use of intensity-modulated radiotherapy: part II. The British Journal of Radiology 2004; 77: 177-182.

6. Cohen JH, Schoenback VJ, Kaufman JS, et al. Racial difference in clinical progression among Medicare recipients after treatment for localized prostate cancer (United States). Cancer Causes Control 2006; 17: 803-811.

7. Latini DM, Elkin EP, Cooperberg MR, et al. Differences in clinical characteristics and disease-free surivival for Latino, African American, and Non-Latino White men with localized prostate cancer: Cancer 2006; 106: 789-795.

8. Chen AB, D'Amico AV, Neville BA, et al. Patient and treatment factors associated with complications after prostate brachytherapy. J Clin Oncol 2006; 24:5298-5304.

9. Trial DB- A clinical Study Data Management System.http://ycmi.med.yale.edu/trialdb. Accessed June 28, 2008.

10. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. March 31, 2003 (http://ctep.cancer.gov), Publish Date: May 22, 2003.

11. Scardino P. Update: NCCN prostate cancer: Clinical practice guidelines. J Natl Comp Canc Netw 2005; 3(Suppl 1): S29-S33.

12. Roach M, Hanks G, Thames H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference: Int J Radiat Oncol Biol Phys. 2006; 65: 965-974.

13. Jani AB, Gratzle J. Analysis of impact of age and race on biochemical control after radiotherapy in different prostate cancer settings. Urology 2005; 66(1):124-9.

14. Connell PP, Ignacio L, Haraf D, et al. Equivalent racial outcome after conformal radiotherapy for prostate cancer: a single departmental experience. J Clin Oncol 2001;19(1):54-61.

15. Johnstone PA, Kane CJ, Sun L, et al. Effect of race on biochemical disease-free outcome in patients with prostate cancer treated with definitive radiation therapy in an equal-access health care system: radiation oncology report of the Department of Defense Center for Prostate Disease Research. Radiology 2002; 225(2):420-6.

16. Young CD, Lewis P, Weinberg V, et al. The impact of race on freedom from prostate-specific antigen failure in prostate cancer patients treated with definitive radiation therapy.
Semin Urol Oncol 2000; 18(2):121-6.

17. Hart KB, Wood DP, Tekyi-Mensah S, et al. The impact of race on biochemical disease-free survival in early-stage prostate cancer patients treated with surgery or radiation therapy.
Int J Radiat Oncol Biol Phys 1999; 45(5):1235-8.

18. U.S. Census Bureau. http://quickfacts.census.gov/qfd/states/09/0952000.html. Accessed September 30, 2008.

19. Gondi V, Deutsch M, O'Toole KM, et al. African-American patients with intermediate-risk prostate cancer have improved biochemical relapse-free survival in a racially diverse university population [Abstract]. Int J Radiat Oncol Biol Phys. 2006; 66: S376-S377.

20. Shenoy PJ, Malik N, Nooka A, et al. Racial differences in the presentation and outcomes of diffuse large B-cell lymphoma in the United States. Cancer 2010.

21. Nichols MA, Mell LK, Hasselle MD, et al. Outcomes in black patients with early breast cancer treated with breast conservation therapy. Int J Radiat Oncol Biol Phys. 2010 (in press).

22. Du XL, Lin CC, Johnson NJ, et al. Effects of individual-level socioeconomic factors on racial disparities in cancer treatment and survival

23. Connell PP, Rotmensch J, Waggoner SE. Race and Clinical Outcome in Endometrial Carcnoma. Obstetrics and Gynecology. 2999; 94: 713-720.

24. Gross CP, Smith BD, Wolf E. Racial disparities in cancer therapy. Cancer. 2008.

25. Steinberg ML. Inequity in Cancer Care: Explanations and solutions for disparity. Seminar in Radiation Oncology. 2008; 18: 161-167.